REMARKS

Interview Summary

During the Interview on August 2, 2004 between Examiner Wax, Dr. Carney and the undersigned, amendment of the claims to recite that the thrombin derivative peptide is a peptide of between 12 and 23 amino acids in length was discussed.

It was also discussed during the interview that the specification does enable and provide written description for the full scope of the angiogenic thrombin derivative peptides recited in the pending claims. Additional evidence that the specification does enable the full scope of the angiogenic thrombin derivative peptides recited in the pending claims was requested by the Examiner.

Claim Amendments

Claims 1, 10, 12, 21 and 22 have been amended to recite that the thrombin derivative peptide is a peptide of between 12 and 23 amino acids in length. This amendment of the claims is also fully supported in the application as filed on July 12, 2001. In particular, the application discloses at page 6, line 15-18, that the thrombin derivative peptide has a sequence of at least 12 amino acids and at page 6, lines 18-20, that thrombin derivative peptide has a sequence of at least 23 amino acids. As such, support is provided in the application for a thrombin derivative peptide of between 12 and 23 amino acids in length.

No new matter is added by the new claims or by the claim amendments.

Enablement

The application as filed enables the full scope of the angiogenic thrombin derivative peptides recited in the pending claims.

In particular, the specification teaches that angiogenic thrombin derivative peptides are compounds which can be employed to induce angiogenic proliferation and migration of endothelial cells resulting in formation of new capillaries and collateral vessels to help restore function to damaged or ischemic heart tissue (see, e.g., page 4, lines 22-24). Angiogenic thrombin derivative peptides possess a thrombin receptor binding domain and a serine esterase conserved sequence (see, e.g., page 6, lines 4-20). The thrombin receptor binding domain

includes a segment of the polypeptide that is capable of selectively binding to the high-affinity thrombin receptor and which includes a sequence of amino acids homologous to a tripeptide cell binding domain of fibronectin (see, e.g., page 6, lines 4-8).

Specific examples of angiogenic thrombin derivative peptides are provided in the specification (see, e.g., page 6, lines 21-28). Particular examples of angiogenic thrombin derivative peptides provided in the specification include polypeptides comprising a thrombin receptor domain having the sequence Arg-Gly-Asp-Ala (SEQ ID NO: 1) together with the serine esterase conserved amino acid sequence Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO: 2), such as the thrombin derivative peptide of SEQ ID NO: 3 (TP508) (see, e.g., page 6, lines 21-25). Other thrombin derivative peptides are disclosed in U.S. Patent Number 5,352,664 and U.S. Patent Number 5,500,412, which are incorporated into the subject application by reference (see specification, e.g., page 2, lines 11-12 and lines 21-22).

Applicant has exemplified the effects of angiogenic thrombin derivative peptide using the thrombin peptide derivative of SEQ ID NO: 3. In particular, Applicant has demonstrated that TP508 has direct angiogenic effects on human endothelial cells causing increased proliferation and migration *in vitro* (Example 1), that exposure of endothelial cells to TP508 has a protective effect to prevent death of cells caused by oxidative exposure, contributing to re-endothelialization and angiogenesis (Example 1), and that TP508 stimulates angiogenesis in a chorioallontoic membrane model (Example 2). Applicant has also demonstrated that TP508 can restore functionality to ischemic heart muscle (Example 3) and stimulate myocardial revascularization (Example 4). Additionally, Applicant has demonstrated that TP508 can significantly suppress restenosis and vascular occlusion (Example 5). As such, Applicant has demonstrated that the thrombin derivative peptide of SEQ ID NO: 3 can promote cardiac tissue repair, stimulate revascularization of cardiac tissue and inhibit restenosis and vascular occlusion.

Thus, since the thrombin derivative peptide of SEQ ID NO: 3 has been shown to promote cardiac tissue repair, stimulate revascularization of cardiac tissue and inhibit restenosis and vascular occlusion, one skilled in the art would reasonably expect that other angiogenic thrombin derivative peptides provided in the specification, particularly polypeptides comprising a thrombin receptor domain together with a serine esterase conserved sequence, can be successfully employed to promote cardiac tissue repair, stimulate revascularization of cardiac tissue and

inhibit restenosis and vascular occlusion. That is, one skilled in the art would accept the assertions in the specification as true and enabling. No evidence has been provided as to why the results achieved using the angiogenic thrombin derivative peptide of SEQ ID NO: 3 (TP508) cannot be correlated to other angiogenic thrombin derivative peptides which comprise a thrombin receptor domain together with a serine esterase conserved sequence, particularly to analogs of TP508.

To provide further evidence that the pending claims are enabled, a Rule 132 Declaration of Darrell H. Carney, Ph.D., inventor, is filed concurrently herewith. The Declaration provides evidence showing that endothelial cells have non-proteolytic high-affinity thrombin receptors (NPARs). Since the subject application discloses data showing that TP508, an NPAR agonist, causes endothelial cell proliferation and migration and cardiac tissue repair and revascularization, it is now apparent that other NPAR agonists would cause the same effect.

The Declaration and its relevance to the claimed invention is discussed in greater detail in the section below.

Declaration of Darrell H. Carney, Ph.D. Under 37 C.F.R. § 1.132

In the Rule 132 Declaration of Dr. Darrell Carney filed concurrently herewith data are disclosed showing that ***endothelial cells have non-proteolytic high-affinity thrombin receptors (NPARs)***. As discussed above, the subject application discloses results which demonstrate that NPAR agonists, such as thrombin derivative peptides, stimulate endothelial cell proliferation and migration (see Example 1). The subject application also discloses results which demonstrate that angiogenic NPAR agonists promote cardiac tissue repair (Example 3), stimulate revascularization of cardiac tissue (Example 4) and inhibit restenosis and vascular occlusion (Example 5). As explained by Dr. Carney in the Declaration, the data indicate that activation of NPAR causes these effects. Because NPAR is present on endothelial cells, these data provide further evidence that one skilled in the art would expect that other NPAR agonists (e.g., other thrombin derivative peptides) can be successfully employed to stimulate endothelial cell proliferation and migration, as well as promote cardiac tissue repair, stimulate revascularization of cardiac tissue and inhibit restenosis and vascular occlusion. As explained by Dr. Carney in the Declaration, since activation of NPAR stimulates endothelial cell proliferation and migration, other NPAR agonists (e.g., thrombin derivative peptides other than TP508) are also expected to

cause endothelial cell proliferation and migration. Accordingly, as explained by Dr. Carney, NPAR agonists (e.g., thrombin derivative peptides other than TP508), e.g., those which act on endothelial cells, are expected to promote cardiac tissue repair, stimulate revascularization of cardiac tissue and inhibit restenosis and vascular occlusion, given the evidence in the application. In particular, thrombin derivative peptides of TP508, such as those recited in U.S. Patent Numbers 5,352,664 and 5,500,412 (e.g., polypeptides of between 12 and 23 amino acids in length comprising a thrombin receptor binding domain and a serine esterase conserved sequence), are also expected to promote cardiac tissue repair, stimulate revascularization of cardiac tissue and inhibit restenosis and vascular occlusion. These two patetns are enclosed herewith as Exhibits F and G.

Terminal Disclaimer

Transmitted concurrently herewith is a Terminal Disclaimer in which the owner of the instant application disclaims, except as provided in the Terminal Disclaimer, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term of any patent on the pending second Application Number 10/050,611, filed on January 16, 2002.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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